Impulse oscillometry bronchodilator response and asthma control

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Clinical implications: IOS is more sensitive than spirometry in detecting bronchodilator response in poorly controlled asthma.

Bronchodilator response (BDR) is conventionally defined as a greater than 12% and greater than 200ml increase from baseline in forced expiratory volume in 1 second (FEV_1) measured using spirometry.[1] Forced expiratory flow between 25-75% of forced vital capacity (FEF_{25-75}) is thought to reflect volume dependent closure of the small airways. Impulse oscillometry (IOS) is an effort-independent forced oscillation technique (FOT) using sound waves superimposed on normal tidal breathing, requiring minimal patient cooperation and is therefore more physiological. Persistent BDR is associated with worse asthma control albeit lung function is often disconnected from patient reported symptoms.[2,3] Due to the ease of performing IOS measurements, IOS BDR threshold had been widely assessed in pediatric pulmonology.[4] However, IOS BDR thresholds in adults are still not clearly defined. We therefore sought to determine the difference between spirometry and IOS BDR in patients with well and poorly controlled asthma.

Retrospectively, we evaluated 57 patients with an established diagnosis of persistent asthma who attended the Scottish Centre for Respiratory Research (Dundee, UK) for screening into clinical trials. Asthma control questionnaire (ACQ-6), fractional exhaled nitric oxide (FeNO) and lung function tests including spirometry (Micromedical, Chatham, United Kingdom) and IOS (Jaeger MasterScreen, Carefusion Technologies) were performed pre and post albuterol 400µg in triplicate according to ERS guidelines, with IOS always performed first.[5] Consents were obtained from all patients for access to their screening data.

We used an ACQ-6 cut point of 1.0 to define poor asthma control.[6] A comparison was made according to pre-defined cut points for IOS BDR values: area under the reactance curve (AX) <35% vs ≥35%; reactance at 5Hz (X5) <15% vs ≥15%; resonance frequency (Fres) <15% vs ≥15% and resistance at 5Hz (R5) <15% vs ≥15%. The comparisons were conducted using Independent Student's T test with alpha error set at 0.05 (2 tailed). Receiver operator characteristic (ROC) curves were plotted to assess sensitivity and specificity of IOS and spirometry % BDR for detecting poor asthma control.

The mean age was 51 years; FEV_1 79% predicted; AX 1.35 kPa/L; R5 0.41 kPa/L/s; R20 0.37 kPa/L/s; R5-R20 0.12 kPa/L/s; ACQ-6 1.38 and FeNO 38 ppb. Mean inhaled corticosteroid (beclomethasone equivalent) dose was 670µg; and 68% were taking LABA; 11% LAMA; 25% LTRA; and 4% theophylline.

Using an ACQ-6 <1 and ≥1 to compare well and poorly controlled asthma, there were significant differences in % BDR with FEV_1, AX, X5, Fres and R5 (Table 1). In the subgroup with a preserved FEV_1 of ≥80% (n=30), % BDR for AX, X5, R5 and FEF_{25-75} were significantly higher in poorly controlled asthma. In the cohort with no spirometry evidence of BDR as represented by a FEV_1 BDR <12% and <200ml (n=37), AX, X5 and R5 were significantly higher in those with poorly controlled asthma. FeNO was also significantly higher in the poorly controlled group.

Asthma control (as mean ACQ-6) was significantly worse comparing % BDR for AX <35% vs ≥35%: 0.92 vs 1.79 (95%CI for difference 0.34, 1.40;p<0.01); X5 <15% vs ≥15%: 0.77 vs 1.73 (CI 0.48, 1.44;p<0.001); Fres <15% vs ≥15%: 0.93 vs 1.76 (CI 0.31, 1.35;p<0.01); R5 <15% vs ≥15%: 0.90 vs 1.79 (CI 0.37, 1.40;p<0.01); and FEV_1 <12% vs ≥12%: 1.22 vs 2.22 (CI 0.26, 1.75;p<0.01).

In patients with preserved FEV_1, ACQ-6 were also significantly higher comparing % BDR for: AX at a cut-point of 35%: 0.73 vs 1.60 (CI 0.25, 1.49;p<0.01); X5 15%: 0.71 vs 1.56(CI 0.26, 1.44;p<0.01); Fres 15%: 0.84 vs 1.52(CI 0.07, 1.29;p<0.05) and R5 15%: 0.81 vs 1.56(CI 0.16, 1.35;p<0.05). These differences in ACQ-6 all exceeded the minimal clinical important difference of 0.5.

ROC curve analysis for predicting poor asthma control with IOS % BDR, namely AX, X5, Fres and R5, demonstrated fair accuracy with AUC between 0.70-0.80 (Table 2). Poor asthma control was detected with a BDR of 35% for AX; 14% for X5; 15% for Fres; and 15% for R5. The corresponding sensitivity and specificity values are shown in Table 2. The AUC were 0.69(CI 0.55, 0.83;$p<0.05$) and 0.66(CI 0.51, 0.80;$p<0.05$), sensitivity: 23% and 45%, specificity: 96% and 77% for FEV_1 12% and 200ml BDR respectively.

Our results demonstrate that IOS % BDR for airway reactance (AX, X5), resonance frequency and resistance at 5Hz were all associated with poor asthma control. This was also observed with FEV_1 but not FEF_{25-75} in all patients, while in those patients with preserved FEV_1 poor control was associated with increased % BDR for FEF_{25-75}. This is consistent with a previous study comparing relative bronchoconstrictor and bronchodilator response using IOS and spirometry in asthma patients.[7] Another study also reported similar findings in asthma with the relative mean percentage change in response to albuterol 400µg being 6% and 34% for FEV_1 and R5 respectively.[8]

Notably the IOS % BDR in the subgroup of asthma patients with preserved FEV_1 was significantly higher in the poorly controlled group. This perhaps reflects that alterations in small airway geometry are more closely related to asthma control. The persistently higher FeNO in the poorly controlled group mirrors underlying type 2 inflammation and is associated with a greater degree of IOS BDR.

A recent study also concluded that the reactance components of FOT were more sensitive than spirometry in detecting poor asthma control.[9] However, they used reference values for FOT BDR derived from healthy subjects which would not be applicable to asthma patients where a greater reversibility would be expected due to alterations in resting bronchomotor tone and airway geometry.

We recognize the main limitation of our study as being retrospective and cross-sectional with a relatively small sample size. However, our findings are consistent with previous studies with larger sample sizes and controlled trials.[7, 8] Our study may have clinical implications suggesting that effort-independent IOS may provide complimentary information on BDR in patients with poorly controlled asthma, especially in those with preserved FEV_1.

In conclusion, bronchodilator response using IOS measurements is associated with poor asthma control. IOS is more sensitive than spirometry in detecting bronchodilator response in poorly controlled asthma especially in those patients with a preserved FEV_1.

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149 Table 1

	Overall		$FEV_1 \geq 80\%$		FEV_1 BDR <12% and <200ml	
	ACQ <1	**ACQ≥1**	**ACQ <1**	**ACQ≥1**	**ACQ <1**	**ACQ≥1**
FEV_1 % BDR	5	8	5	6	4	4
		*(1, 6)		(-4, 1)		(-3, 1)
FEF_{25-75} % BDR	12	17	9	22	11	16
		(-12, 2)		**(-21, -4)		(-13, 3)
AX % BDR	26	49	22	45	22	43
		***(11, 34)		*(5, 40)		**(6, 35)
X5 % BDR	12	28	7	28	9	25
		***(8, 25)		**(9, 33)		**(4, 26)
Fres % BDR	14	22	13	19	13	19
		*(1, 14)		(-4, 15)		(-14, 1)
R5 % BDR	10	19	8	18	9	18
		**(4, 14)		**(4, 17)		**(3, 15)
R20 % BDR	10	12	7	13	8	12
		(-2, 7)		(0.26, 11)		(-10, 2)
R5-R20 % BDR	-27	39	23	34	26	31
		(-6, 30)		(-15, 38)		(-28, 18)
FeNO ppb	25	49	22	52	24	46
		**(10, 37)		*(8, 52)		*(3, 41)

ACQ = Asthma control questionnaire-6, BDR = bronchodilator response, FEV_1 = forced expiratory volume in 1st second, FEF_{25-75} = forced expiratory volume at 25-75% of forced vital capacity, AX = area under the reactance curve, X5 = reactance at 5Hz, Fres = resonance frequency, R5 = resistance at 5Hz, R20 = resistance at 20Hz, R5-R20 = difference in resistance at 5 and 20 Hz, FeNO = fractional exhaled nitric oxide. Values are presented as mean (95% CI for difference). * p<0.05, ** p<0.01, ***p<0.001

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152 Table 2

	% BDR	% sensitivity	% specificity	AUC (95% CI)
R5	15	77	73	0.77 (0.63, 0.91)**
AX	35	77	73	0.78 (0.65, 0.91)***
X5	14	84	61	0.76 (0.63, 0.89)**
Fres	15	71	65	0.71 (0.57, 0.86)**

BDR = bronchodilator response, AX = area under the reactance curve, X5 = reactance at 5Hz, Fres = resonance frequency, R5 = resistance at 5Hz, AUC = area under the curve, CI = confidence interval. * p<0.05, ** p<0.01, ***p<0.001.

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